[redacted]

Claim 10. (Amended) [Purified] A hepatitis C virus (HCV) preparation wherein said HCV is isolated from the cellular constituents with which it is normally associated.

REMARKS

Claim 10 as amended is pending in this application and is presented for reconsideration.

Regarding Amendments to the Claims:

Claim 10 has been amended to recite an HCV preparation isolated from the cellular constituents with which HCV is normally associated, in order to clarify the meaning of the term "purified HCV". Support for this amendment can be found in the specification at page 36, lines 17-21. No new matter has been added by this amendment.

Provisional Double Patenting Rejection:

Claim 10 has been rejected under 35 U.S.C. § 101 for allegedly claiming the same invention as claim 10 of copending application No. 08/440,755. Applicants intend to cancel claim 10 in the '755 application in their response to the outstanding office action in that case. Accordingly, applicants respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. § 112, Second Paragraph Rejection:

Claim 10 has been rejected under 35 U.S.C. § 112, second paragraph, because the claim allegedly fails to particularly point out and specifically claim the subject matter which applicants regard as the invention. In particular, the Examiner stated that the metes and bounds of "purified HCV" were unclear. This language no longer appears in the claim, which now specifically recites the level of purification of the virus. Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

35 U.S.C. § 112, First Paragraph Rejection:

Claim 10 has been rejected under 35 U.S.C. § 112, first paragraph, because the claim allegedly contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention. Applicants respectfully traverse this rejection. Methods for purifying HCV so that it is "isolated from the cellular constituents with which HCV is normally associated" are described in the specification at, *inter alia*, pages 68-74, and methods of growing the virions in cell culture are described at pages 74-77. The alleged presence of soluble HCV polypeptides in these preparations as suggested by the Examiner are not relevant. Accordingly, applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

35 U.S.C. § 102 Rejections:

Claim 10 was rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Prince *et al.* The Lancet, 10 November 1984, pp. 1071–1075. Similarly, claim 10 was rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by two Seto *et al.* References (U.S. Patent Nos. 4,673,634 and 4,707,439), Coursaget (U.S. Patent No. 4,464,474), and Wands (U.S. Patent No. 4,870,026). However, none of these references report the sucessful isolation of purified HCV.

Prince et al. report a putative non-A, non-B hepatitis (NANB) virus. The virus was identified in primary cultures of hepatocytes which had been inoculated with sera from various patients and chimpanzees showing symptoms of NANB infection. Identification and characterization of the virus, and of replicating species of the virus was by electron microscopy. The diameter of the virus (85–90nm) is substantially larger than the largest reported diameter of HCV (60nm). These observations of Prince et al. were later refuted by McCaul et al. The Lancet, April 13, 1985, pp. 868-869, where they observed membrane alterations in uninfected hepatocyte cultures which resemble the membrane alterations reported by Prince.

Seto et al. disclose a putative NANB associated antigen in the '634 patent, which is reportedly present on the surface of virus particles "at a density of 1.14 g/ml". The claims are directed towards the isolated antigen, antibodies specifically reactive to the antigen, a pharmaceutical composition comprised of an immunogenic amount of the antigen, and a kit for screening or detecting a carrier of NANBH, comprised of the purified antigen. Although the

reported antigen is purified from serum, there have been no reports of HCV antigens being purified from serum.

However, a separate reference, Seto and Gerety, *Proc Nat'l Acad Sci USA* (1985) **82**:4934–4938 describes a serologic marker associated with NANBH, a glycoprotein which was isolated from the serum of a patient with NANBH, with physical characteristics as discussed on page 4936. The reference also describes preparation of monkey antiserum to the glycoprotein and a solid phase RIA utilizing the monkey immune serum (page 4935). The RIA showed that only 17 of 42 NANB patients were positive for this antigen. The anti-gp antibody also reacts with disrupted HTLV (Table 3). Thus, the authors suggest that the etiologic agent for NANBH is a retrovirus, quite unlike HCV.

Coursaget (the '474 patent) describes a particle purportedly found in body fluids from NANB hepatitis patients. It is stated that the particle resembles a togavirus, ranges from 50 to 60 nm in diameter and has a core particle size of about 40 nm. This particle, which is clearly not an HCV particle, is also described in Coursaget *et al.*, *Lancet* (1979) 2:92.

First, Coursaget's work has not been accepted as having identified the etiologic agent of parenterally transmitted NANB hepatitis (pt-NANBH). U.S. Patent No. 4,702,909 issued to Villarejos et al. (the '909 patent, having priority dates in 1984 and 1982) dismissed the Coursaget particle as the etiologic agent of parentally transmitted NANBH, stating (column 2, lines 8 to 14, 45 to 53):

> In 1979 Coursaget et al., described 60 nm particles resembling toga-virus found in urine and sometimes in serum of non-A, non-B hepatitis. None of these particles have been shown to be consistently associated with the illness; therefore, it has been concluded that the specific agent of non-A, non-B hepatitis has not yet been discovered.... This subject has been reviewed by R.J. Gerety (Non-A, Non-B Hepatitis, Academic Press, 1981, Chapter 13, pp 207-228 [Exhibit 8]), who concludes that neither viral particles nor antigens specific for non-A, non-B hepatitis have yet been positively identified. In summary, it is apparent that no specific relationship to non-A, non-B hepatitis infection can be claimed for the diverse particles and antigens found up until now.

In addition, Dienstag, *Gastroenterology* (1983) 85:743-68, reported on a number of virus-like particles described in materials from patients and experimental animals with NANBH which

implicated donors or blood products. The particles described by Coursaget in the Lancet article appear in this report. Regarding these particles, Dienstag concluded (at 748 and 751):

> [D]espite a plethora of reports to the contrary, no viral agent or immunologic marker has been identified that fulfills accepted serologic criteria for a specific association with NANB hepatitis.... No serologic relationship between these particles and NANB hepatitis, however, has been demonstrated, and the multiplicity of virus types and sizes observed underscores the caution with which these reports must be interpreted. Those who have extensive experience with electron microscopy of human tissues and fluids are well aware of the ubiquity of visual artifacts and virus-like particles in these materials.

The workers in the NANBH field clearly considered the work reported in the '474 patent to be a false lead.

Second, the '474 patent itself states that the particle was unexpectedly found in urine with more consistency than in serum. It was not found in serum from acute NANBH patients, and was found in serum from only one of eight hemodialysis patients with elevated serum glutamate-pyruvate transaminase activity. [Column 2, line 52 to column 3, line 10]. However, using a PCR assay for the presence of the viral RNA (which is indicative of the presence of virus), it has been found that HCV is always detectable in acute phase serum of HCV infected chimpanzees. Farci, *et al.*, J. Infectious Diseases (1992) 165:1006-1011. It has also been reported that 81% of patients with chronic liver disease and positive by immunoassay for anti-HCV antibodies were positive for HCV RNA in serum. Of those patients that were positive for HCV RNA in the serum, only 7% were positive for HCV RNA in urine. Liou *et al.*, J. Med. Virol. (1992) 37:197-202. Thus, HCV is present in all or the majority of acute phase and chronic phase sera and only a minority of urine samples; Coursaget's antigen exhibits the opposite behaviour.

Finally, the '474 patent reports a core particle size of about 40 nm in diameter. In contrast, Takahashi et al. report a size of 33 nm for HCV core particles. (The 33 nm particles were reportedly identified as *bona fide* HCV particles by immunoassay, as well as by identification of HCV RNA.) Takahashi et al., Virology 191:431-434 (1992). Measurement of particle size by electron microscopy is usually fairly precise, typically within 1 nm. For example, the particle sizes of other hepatitis agents have all been determined to two significant figures; i.e., HAV particles are 27 nm, HDV particles are 36 nm, Dane particles (HBV) are 40 nm, and

hepatitis B surface antigen particles (HBsAg) are 26 nm. Thus, the difference in size between the Coursaget core particle (40 nm) and the reported HCV core particle (33 nm) is significant.

Clearly the particle described by Coursaget in the '474 patent is not the etiologic agent of HCV infection discovered by applicants. Thus, the Examiner is respectfully requested to reconsider and withdraw this rejection under 35 U.S.C. § 102(b) over the '474 patent.

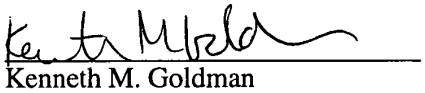
Wands discusses hepatitis viruses in general, but in fact discloses only the hepatitis B surface antigen. Wands never discloses the isolation or discovery of, let alone the purification of, *any* etiologic agent for non-A, non-B hepatitis. Accordingly, Wands cannot teach or disclose that which was not even discovered until the present invention.

Accordingly, applicants request that the Examiner withdraw the rejections under 35 U.S.C. § 102.

CONCLUSION:

Applicants submit that the pending claim is not anticipated under 35 U.S.C. §102, and comports with the requirements of 35 U.S.C. §112, first and second paragraphs. Accordingly, applicants believe that this case is now in condition for allowance, and respectfully solicit the Examiner to expedite prosecution of the patent application to finality. Should the Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

By: 

Kenneth M. Goldman
Attorney for Applicants
Reg. No. 34,174

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CHIRON CORPORATION
4560 Horton Street
Emeryville, California 94608
(510) 923-2719